Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 2938–2942

Stereoselective synthesis of a C_{19}–C_{26} fragment of amphidinolides G and H

Pilar Formentín,[b] Juan Murga,[a,*] Miguel Carda[a] and J. Alberto Marco[b]

[a]*Depart. de Q. Inorgánica y Orgánica, Univ. Jaume I, 12071 Castellón, Spain*
[b]*Depart. de Q. Orgánica, Univ. de Valencia, 46100 Burjassot, Valencia, Spain*

Received 9 October 2006; accepted 20 October 2006
Available online 15 November 2006

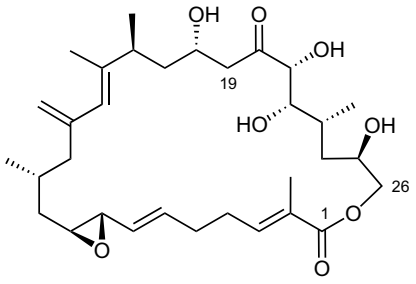
Abstract—A short, stereoselective synthesis of the C_{19}–C_{26} segment of the structure of the cytotoxic macrolides amphidinolides G and H is reported. A precursor from the chiral pool has been used as the starting material.

1. Introduction

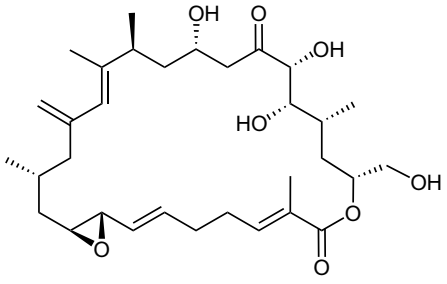
Marine microorganisms belonging to several phyla have attracted the attention of natural product chemists because of their role as the actual producers of many bioactive metabolites, initially found in, and deemed specific to, various marine macroorganisms.[1] Amongst these metabolites, the amphidinolides are a family of macrolides isolated from marine dinoflagellates of the *Amphidinium* genus that are symbiotic to *Amphiscolops* flatworm species.[2] These macrolides have been found to display a range of pharmacological properties, most particularly cytotoxicity against several tumoral cell lines. Amphidinolides B, G, H, and N have been shown to be very potent in this aspect ($IC_{50} < 1$ nm), a feature which renders them promising for cancer chemotherapy. In the case of amphidinolide H, its pharmacological action has been related to its ability to covalently bind on actin subdomain 4 with subsequent stabilization of the actin filaments.[3]

2. Results and discussion

In view of the aforementioned pharmacological properties, it is not surprising that the amphidinolides have attracted considerable interest from the synthetic community. In fact, total syntheses of amphidinolides A,[4] J,[5] K,[6] P,[7,8] T,[9] W,[10] and X[11] have already been reported. We have recently started a research project aimed at the stereoselective synthesis of the highly potent amphidinolides G and H (Fig. 1). Hydrolytic lactone ring-opening of these two isomeric macrolides would give the same open-chain hydroxy acid. Herein, we report a short synthesis of a C_{19}–C_{26} fragment common to the two natural compounds.[12] This fragment corresponds to compound **1**, which contains four out of the nine sp^3 stereocenters of both amphidinolides. Our retrosynthetic analysis for **1** is shown in Scheme



Amphidinolide G

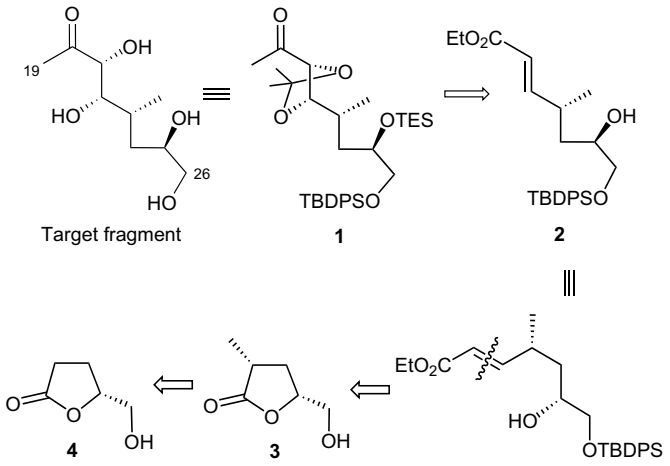


Amphidinolide H

Figure 1. Proposed structures of amphidinolides G and H.

* Corresponding author. Tel.: +34 964 728174; fax: +34 964 728214; e-mail: jmurga@qio.uji.es

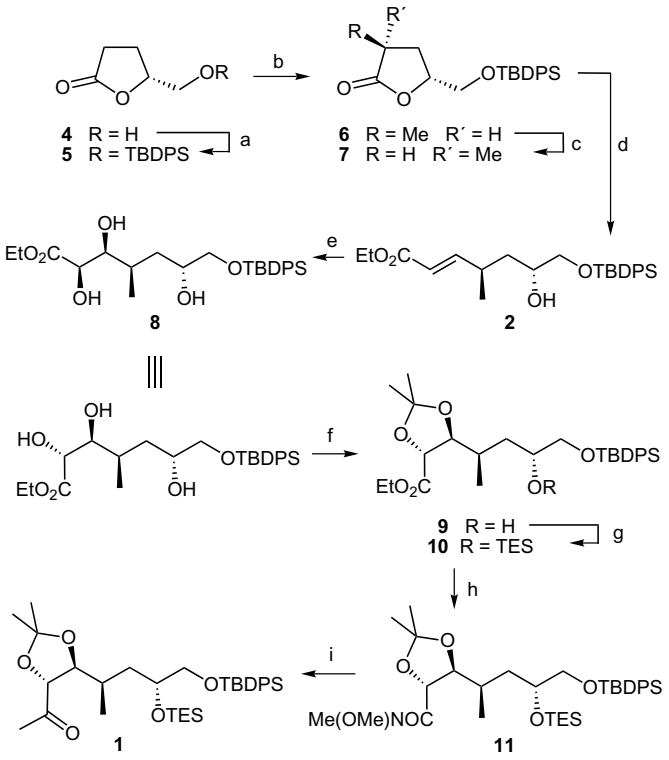
0957-4166/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetasy.2006.10.024



Scheme 1. Retrosynthetic analysis of the target C_{19}–C_{26} compound **1**.

1 and relies on a starting material from the chiral pool, the known lactone **4**.

Scheme 2 depicts the actual synthetic sequence which led to **1**. Compound **7**, a silylated derivative of lactone **3** (Scheme 1) was obtained with an improved yield by means of a modified procedure. Thus, lactone **4**, prepared as described from D-glutamic acid,[13,14] was first silylated[15] to **5** and then methylated via the lithium enolate.[13,16] This gave lactone **6**[13] in 80% yield as the major component of a 92:8 mixture with its diastereomer **7**. The mixture was enolized again and kinetically protonated at a low temperature with a sterically hindered proton donor.[17,18] In this way, a 96:4 mixture of **7** (major) and **6** was obtained. DIBAL reduction of **7** gave an aldehyde, which was immediately subjected to Wittig olefination. The resulting *E*-ester **2** was then submitted to a Sharpless asymmetric dihydroxylation,[19] which provided trihydroxy ester **8** as a single stereoisomer. Protection of the vicinal diol as an acetonide, followed by silylation of the remaining free alcohol, furnished compound **10**, with all the stereogenic centers already in place. Hydrolysis of the ethyl ester group was performed under mild conditions,[20] due to the potential base sensitivity of the silyl groups. The resulting acid was then converted into the Weinreb amide **11**.[21] Finally, treatment of the latter with methylmagnesium bromide provided the desired methyl ketone **1**.[22]



Scheme 2. Reagents and conditions: (a) Ref. 15; (b) LDA, THF, −78 °C, 40 min, then MeI, −78 °C, 2 h, then TBDPSCl, NEt_3, −78 °C, 30 min, 80% overall (dr 92:8); (c) LDA, THF, −78 °C, 40 min, then 2,6-di-*tert*-butylphenol, −78 °C, 1 h, then TBDPSCl, NEt_3, −78 °C, 30 min (dr 96:4), followed by chromatographic separation, 67% overall; (d) DIBAL, CH_2Cl_2, −78 °C, 30 min, then $Ph_3P{=}CHCO_2Et$, toluene, 80 °C, 16 h (*E*/*Z*, 93:7), followed by chromatographic separation, 85%; (e) AD-mix-α, $MeSO_2NH_2$, aq *tert*-BuOH, 0 °C, 18 h, 95%; (f) 2,2-dimethoxypropane, CSA, 3 Å MS, acetone, rt, 18 h, 76%; (g) TESOTf, 2,6-lutidine, CH_2Cl_2, rt, 1 h, 97%; (h) Me_3SiOK, THF, rt, 1 h, then MeNH(OMe)HCl, NMM, EDAC, CH_2Cl_2, rt, 18 h, 89% overall; (i) MeMgBr, THF, 0 °C, 1 h, 81%. Abbreviations and acronyms: TBDPS, *tert*-butyldiphenylsilyl; CSA, camphorsulfonic acid; TES, triethylsilyl; EDAC, *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride; NMM, *N*-methylmorpholine.

3. Conclusions

A short, stereoselective synthesis of the C_{19}–C_{26} fragment of the cytotoxic macrolides amphidinolides G and H has been achieved. Studies toward the total synthesis of both natural lactones are underway.

4. Experimental

4.1. General

NMR spectra were measured at 500 MHz in $CDCl_3$ solution at 25 °C. The signals of the deuterated solvent ($CDCl_3$) were taken as the reference (the singlet at δ 7.25 for ^1H NMR and the triplet centered at 77.00 ppm for ^{13}C NMR data). The multiplicities of the ^{13}C NMR signals were determined with the DEPT pulse sequence. Mass spectra were run by the electron impact (EIMS, 70 eV) or with the fast atom bombardment mode (FABMS, *m*-nitrobenzyl alcohol matrix) on a VG AutoSpec mass spectrometer. IR data are only given for compounds with relevant functions (OH, C=O) and were recorded as oily films on NaCl plates (oils) or as KBr pellets (solids). Optical rotations were measured at 25 °C. Reactions which required an inert atmosphere were carried out under N_2 with flame-dried glassware. Et_2O and THF were freshly distilled from sodium-benzophenone ketyl. Dichloromethane was freshly distilled from CaH_2. Commercially available reagents were used as received. Unless detailed otherwise, 'work-up' means pouring the reaction mixture into 5% aq $NaHCO_3$ (if the reaction was carried out in an acidic medium) or into satd aq NH_4Cl (if it was carried out in a basic medium), extraction with the indicated solvent, then washing again the organic layer with brine, drying over anhydrous Na_2SO_4 or $MgSO_4$ and elimination

of the solvent in vacuo. When the solutions were filtered through a Celite pad, the pad was additionally washed with the same solvent, and the washing liquids were incorporated to the main organic layer. The material obtained was then chromatographed on a silica gel column (60–200 μm) with the indicated eluent.

4.2. (3*S*,5*R*)-5-(*tert*-Butyldiphenylsilyloxymethyl)-3-methyldihydrofuran-2(3*H*)-one, 6

Lactone **5** (2.13 g, 6 mmol) was dissolved in dry THF (120 mL) and treated at −78 °C under N_2 with LDA (9.0 mL of a 2 M solution in THF, 18 mmol). The reaction mixture was then stirred for 40 min at −78 °C, followed by the addition of MeI (2.25 mL, 36 mmol). After stirring at −78 °C for 2 h, Et_3N (530 μL, 3.8 mmol), and TBDPSCl (780 μL, 3.0 mmol) were added and the stirring was continued for 30 min at −78 °C. Work-up (extraction with EtOAc) and column chromatography on silica gel (hexanes–Et_2O, 95:5) yielded **6**[13] (1.77 g, 80%) as a 92:8 mixture with **7**, which was used as such in the next step.

4.3. (3*R*,5*R*)-5-(*tert*-Butyldiphenylsilyloxymethyl)-3-methyldihydrofuran-2(3*H*)-one, 7

The **6**/**7** lactone mixture from above (1.47 g, 4 mmol) was dissolved in dry THF (80 mL) and treated at −78 °C under N_2 with LDA (6.0 mL of a 2 M solution in THF, 12 mmol). The reaction mixture was then stirred for 40 min at −78 °C, followed by addition of 2,6-di-*tert*-butylphenol (4.95 g, ca. 24 mmol). After stirring at −78 °C for 1 h, Et_3N (350 μL, 2.5 mmol) and TBDPSCl (520 μL, 2.0 mmol) were added and stirring was continued for 30 min at −78 °C. Work-up (extraction with EtOAc) and column chromatography on silica gel (hexanes–Et_2O, 95:5) afforded pure **7** (985 mg, 67%). Solid, mp 85–86 °C, $[\alpha]_D = -13.4$ (*c* 1.1, $CHCl_3$); IR ν_{max} (cm^{-1}) 1767 (C=O); δ_H (500 MHz, $CDCl_3$): 7.70–7.65 (4H, m), 7.50–7.40 (6H, m), 4.47 (1H, m), 3.87 (1H, dd, $J = 11.5$, 3.5 Hz), 3.75 (1H, dd, $J = 11.5$, 3.5 Hz), 2.68 (1H, m), 2.39 (1H, m), 1.85 (1H, m), 1.30 (3H, d, $J = 7.0$ Hz), 1.06 (9H, s); δ_C (125 MHz, $CDCl_3$): 179.4, 133.1, 132.9, 19.2 (C), 135.6 (×2), 135.5 (×2), 129.8 (×2), 127.8 (×4), 78.1, 32.1 (CH), 64.7, 35.4 (CH_2), 26.8 (×3), 15.4 (CH_3). HR FABMS *m*/*z* 369.1911 [M+H^+], calcd for $C_{22}H_{29}O_3Si$, 369.1886. Anal. Calcd for $C_{22}H_{28}O_3Si$: C, 71.83; H, 8.39. Found: C, 71.84; H, 8.35.

4.4. (4*R*,6*R*)-7-(*tert*-Butyldiphenylsilyloxy)-6-hydroxy-4-methylhept-2*E*-enoic acid ethyl ester, 2

Lactone **7** (920 mg, 2.5 mmol) was dissolved in dry CH_2Cl_2 (15 mL) and treated at −78 °C under N_2 with DIBAL (2.75 mL of a 1 M solution in hexane, 2.75 mmol). The reaction mixture was then stirred for 30 min at −78 °C. After this time, MeOH was added (2 mL), with subsequent stirring for 1 h. Work-up (extraction with AcOEt) and solvent removal in vacuo provided a crude lactol that was employed as such in the following step. It was dissolved in dry toluene (15 mL) and treated with Ph_3P=CHCOOEt (1.22 g, 3.5 mmol). The reaction mixture was then stirred for 16 h at 80 °C. Solvent removal under reduced pressure provided a crude oil containing a 93:7 mixture of the *E*/*Z* stereoisomers. Careful column chromatography of the residue on silica gel (hexanes–EtOAc, 80:20) provided *E*-**2** (936 mg, 85%). Oil, $[\alpha]_D = -14.0$ (*c* 0.9, $CHCl_3$); IR ν_{max} (cm^{-1}) 3490 (br, OH), 1716 (C=O); δ_H (500 MHz, $CDCl_3$): 7.70–7.65 (4H, m), 7.50–7.40 (6H, m), 6.90 (1H, dd, $J = 15.7$, 7.5 Hz), 5.74 (1H, dd, $J = 15.7$, 1.1 Hz), 4.19 (2H, q, $J = 7.0$ Hz), 3.78 (1H, m), 3.67 (1H, dd, $J = 10.0$, 3.5 Hz), 3.49 (1H, dd, $J = 10.0$, 7.2 Hz), 2.49 (1H, sext, $J = 7.0$ Hz), 2.45 (OH, d, $J = 4.0$ Hz), 1.60 (1H, m), 1.33 (1H, m), 1.30 (3H, t, $J = 7.0$ Hz), 1.08 (9H, s), 1.05 (3H, d, $J = 6.5$ Hz); δ_C (125 MHz, $CDCl_3$): δ 166.8, 133.1 (×2), 19.3 (C), 154.1, 135.5 (×4), 129.9 (×2), 127.8 (×4), 119.5, 69.5, 32.8 (CH), 68.0, 60.2, 38.7 (CH_2), 26.9 (×3), 18.9, 14.3 (CH_3). HR-EIMS *m*/*z* (%) = 383.1642 (M^+−*t*-Bu, 2), 337 (16), 199 (100). Calcd for $C_{26}H_{36}O_4Si$–*t*-Bu, 383.1678. Anal. Calcd for $C_{26}H_{36}O_4Si$: C, 70.87; H, 8.23. Found, C, 70.92; H, 8.19.

4.5. (2*R*,3*S*,4*R*,6*R*)-7-(*tert*-Butyldiphenylsilyloxy)-2,3,6-trihydroxy-4-methylheptanoic acid ethyl ester, 8

Ethyl ester **2** (881 mg, 2 mmol) was dissolved in a mixture of *tert*-BuOH (10 mL) and water (10 mL). AD-mix-α (8.4 g) and $MeSO_2NH_2$ (570 mg, 6 mmol) were then added at 0 °C. The reaction mixture was then stirred for 18 h at the same temperature. After this time, Na_2SO_3 (3 g) was added, with subsequent stirring for 45 min. Work-up (extraction with CH_2Cl_2) and column chromatography on silica gel (hexanes–EtOAc, 40:60) furnished trihydroxy ester **8** (902 mg, 95%). Oil, $[\alpha]_D = +9.1$ (*c* 1.5, $CHCl_3$); IR ν_{max} (cm^{-1}) 3440 (br, OH), 1738 (C=O); δ_H (500 MHz, $CDCl_3$): 7.70–7.65 (4H, m), 7.45–7.35 (6H, m), 4.26 (3H, m), 3.82 (1H, m), 3.69 (1H, m), 3.63 (1H, dd, $J = 10.0$, 3.8 Hz), 3.51 (1H, dd, $J = 10.0$, 7.3 Hz), 3.40 (OH, br s), 3.00 (OH, br s), 2.90 (OH, br s), 2.04 (1H, br heptuplet, $J = 7.0$ Hz), 1.63 (1H, ddd, $J = 14.5$, 10.3, 5.0 Hz), 1.30 (3H, t, $J = 7.0$ Hz), 1.23 (1H, ddd, $J = 14.5$, 8.5, 2.3 Hz), 1.08 (9H, s), 1.05 (3H, d, $J = 7.0$ Hz); δ_C (125 MHz, $CDCl_3$): 173.8, 133.2 (×2), 133.1 (×2), 19.2 (C), 135.5 (×4), 129.8 (×2), 127.7 (×2), 76.1, 71.3, 70.4, 34.0 (CH), 68.5, 61.9, 36.1, (CH_2), 26.9 (×3), 16.1, 14.1 (CH_3). HR FABMS *m*/*z* 497.2341 [M+Na^+], calcd for $C_{26}H_{38}O_6SiNa$, 497.2335. Anal. Calcd for $C_{26}H_{38}O_6Si$: C, 65.79; H, 8.07. Found, C, 65.74; H, 7.98.

4.6. (4*R*,5*S*)-5-[(2*R*,4*R*)-5-(*tert*-Butyldiphenylsilyloxy)-4-hydroxypent-2-yl]-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid ethyl ester, 9

Trihydroxy ester **8** (712 mg, 1.5 mmol) was dissolved in a mixture of acetone (15 mL) and 2,2-DMP (4 mL) and treated with camphorsulfonic acid (23 mg, 0.1 mmol) and 3 Å MS (500 mg). The reaction mixture was then stirred for 18 h and filtered through a pad of Celite. Removal of all volatiles in vacuo and column chromatography of the residue on silica gel (hexanes–EtOAc, 70:30) provided alcohol **9** (587 mg, 76%). Oil, $[\alpha]_D = -2.0$ (*c* 1.7, $CHCl_3$); IR ν_{max} (cm^{-1}) 3530 (br, OH), 1753 (C=O); δ_H (500 MHz, $CDCl_3$): 7.70–7.65 (4H, m), 7.45–7.35 (6H, m), 4.30–4.20 (3H, m), 4.13 (1H, dd, $J = 7.0$, 4.8 Hz), 3.85 (1H, m), 3.67 (1H, dd, $J = 10.0$, 3.5 Hz), 3.52 (1H, dd, $J = 10.0$, 7.3 Hz), 2.50 (OH, d, $J = 3.5$ Hz), 2.16 (1H, m), 1.58 (1H, ddd, $J = 14.0$, 10.0, 3.8 Hz), 1.45 (3H, s), 1.43 (3H, s), 1.28

(3H, t, $J = 7.0$ Hz), 1.23 (1H, m), 1.10 (9H, s), 1.01 (3H, d, $J = 7.0$ Hz); δ_C (125 MHz, $CDCl_3$): 171.5, 133.2 (×2), 110.8, 19.2 (C), 135.5 (×4), 129.8 (×2), 127.7 (×2), 83.1, 76.8, 69.4, 31.7 (CH), 68.6, 61.2, 36.2, (CH_2), 26.9 (×4), 25.6, 14.1, 13.8 (CH_3). HR EIMS *m/z* (% rel. int.) 499.2522 (M^+−Me, 1), 453 (10), 399 (30), 325 (80), 241 (73), 199 (100). Calcd for $C_{29}H_{42}O_6Si$–Me, 499.2516. Anal. Calcd for $C_{29}H_{42}O_6Si$: C, 67.67; H, 8.22. Found, C, 67.60; H, 8.14.

4.7. (4*R*,5*S*)-5-[(2*R*,4*R*)-5-(*tert*-Butyldiphenylsilyloxy)-4-(triethylsilyloxy)pent-2-yl]-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid ethyl ester, 10

Ester **9** (515 mg, 1.0 mmol) was dissolved under N_2 in dry CH_2Cl_2 (10 mL) and treated sequentially with 2,6-lutidine (175 μL, 1.5 mmol) and TESOTf (270 μL, 1.2 mmol). The reaction mixture was then stirred for 1 h at room temperature and worked up (extraction with CH_2Cl_2). Column chromatography on silica gel (hexane–EtOAc, 80:20) gave ester **10** (610 mg, 97%). Oil, $[\alpha]_D = +7.1$ (*c* 1.6, $CHCl_3$); IR ν_{max} (cm^{-1}) 1758 (C=O); δ_H (500 MHz, $CDCl_3$): 7.70–7.65 (4H, m), 7.45–7.35 (6H, m), 4.30 (1H, d, $J = 6.7$ Hz), 4.30–4.20 (2H, m), 4.10 (1H, dd, $J = 6.5$, 5.5 Hz), 3.80 (1H, m), 3.62 (1H, dd, $J = 10.0$, 5.0 Hz), 3.48 (1H, dd, $J = 10.0$, 7.0 Hz), 2.04 (1H, m), 1.64 (1H, ddd, $J = 13.5$, 10.3, 3.0 Hz), 1.55 (1H, ddd, $J = 13.5$, 8.8, 3.3 Hz), 1.48 (3H, s), 1.46 (3H, s), 1.29 (3H, t, $J = 7.0$ Hz), 1.08 (9H, s), 1.03 (3H, d, $J = 7.0$ Hz), 0.90 (9H, t, $J = 8$ Hz), 0.52 (6H, q, $J = 8$ Hz); δ_C (125 MHz, $CDCl_3$): 171.6, 133.6 (×4), 110.9, 19.2 (C), 135.5 (×4), 129.6 (×2), 127.6 (×4), 83.7, 77.1, 70.6, 31.7 (CH), 68.2, 61.2, 38.4, 5.0 (×3) (CH_2), 27.1, 26.9 (×3), 25.8, 14.3, 14.1, 6.8 (×3), (CH_3). HR EIMS *m/z* (% rel. int.) 613.3429 (M^+−Me, 10), 571 (13), 313 (100), 183 (86), 169 (84), 135 (70). Calcd for $C_{35}H_{56}O_6Si_2$–Me, 613.3380. Anal. Calcd for $C_{35}H_{56}O_6Si_2$: C, 66.83; H, 8.97. Found, C, 66.75; H, 8.84.

4.8. (4*R*,5*S*)-5-[(2*R*,4*R*)-5-(*tert*-Butyldiphenylsilyloxy)-4-(triethylsilyloxy)pent-2-yl]-2,2-dimethyl-1,3-dioxolane-4-carboxylic acid *N*-methoxy-*N*-methylamide, 11

Ethyl ester **10** (503 mg, 0.8 mmol) was dissolved in dry THF (30 mL). Then, TMSOK (1.54 g, 12 mmol) was added, with subsequent stirring for 1 h. A solution of saturated aqueous citric acid was then added, and the stirring continued for 20 min at room temperature. After this time, work-up (extraction with EtOAc) and evaporation under reduced pressure provided a crude oily acid that was used directly in the next step.

The crude compound from above was dissolved under N_2 in dry CH_2Cl_2 (30 mL) and treated sequentially at 0 °C with NMM (264 μL, 2.4 mmol), EDAC (460 mg, 2.4 mmol) and Me(MeO)NH·HCl (234 mg, 2.4 mmol). The reaction mixture was stirred for 18 h at room temperature. Work-up (extraction with CH_2Cl_2) and column chromatography on silica gel (hexane–AcOEt, 90:10) yielded **11** (458 mg, 89%). Oil, $[\alpha]_D = +13.2$ (*c* 1.1, $CHCl_3$); IR ν_{max} (cm^{-1}) 1674 (C=O); δ_H (500 MHz, $CDCl_3$): 7.70–7.65 (4H, m), 7.45–7.35 (6H, m), 4.58 (1H, br s), 4.32 (1H, m), 3.76 (1H, m), 3.72 (3H, s), 3.58 (1H, dd, $J = 10.0$, 4.7 Hz), 3.43 (1H, dd, $J = 10.0$, 7.0 Hz), 3.21 (3H, br s), 1.99 (1H, m), 1.58 (1H, ddd, $J = 14.0$, 10.5, 2.5 Hz), 1.47 (6H, s), 1.37 (1H, ddd, $J = 14.0$, 9.2, 2.5 Hz), 1.05 (9H, s), 1.01 (3H, d, $J = 6.8$ Hz), 0.88 (9H, t, $J = 8$ Hz), 0.50 (6H, q, $J = 8$ Hz); δ_C (125 MHz, $CDCl_3$): 176.0 (br), 133.7, 133.6, 110.5, 19.2 (C), 135.6 (×4), 129.6 (×2), 127.7 (×4), 82.7, 74.7 (br), 70.6, 31.6 (CH), 68.4, 38.3, 5.0 (×3) (CH_2), 61.6 (br), 32.4 (br), 27.3, 26.9 (×3), 26.2, 15.0, 6.9 (×3) (CH_3). HR FABMS *m/z* 644.3835 [M+H^+], calcd for $C_{35}H_{58}NO_6Si_2$, 644.3803. Anal. Calcd for $C_{35}H_{57}NO_6Si_2$, C, 65.28; H, 8.92. Found, C, 65.18; H, 8.87.

4.9. 1-{5-[(2*R*,4*R*)-5-(*tert*-Butyldiphenylsilyloxy)-4-(triethylsilyloxy)pent-2-yl]-(4*R*,5*S*)-2,2-dimethyl-[1,3]dioxolan-4-yl}-ethanone, 1

Amide **11** (322 mg, 0.5 mmol) was dissolved under N_2 at 0 °C in dry THF (5 mL) and treated with MeMgBr (500 μL of a 3 M solution in Et_2O, 1.5 mmol). The reaction mixture was then stirred for 1 h at 0 °C and worked up (extraction with AcOEt). Column chromatography on silica gel (hexane–EtOAc, 95:5) provided ketone **1** (242 mg, 81%). Oil, $[\alpha]_D = +17.7$ (*c* 0.8, $CHCl_3$); IR ν_{max} (cm^{-1}) 1720 (C=O); HR FABMS *m/z* 599.3586 [M+H^+], calcd for $C_{34}H_{55}O_5Si_2$, 599.3588. Anal. Calcd for $C_{34}H_{54}O_5Si_2$: C, 68.18; H, 9.09. Found, C, 68.07; H, 8.99. For NMR data see Ref. 22.

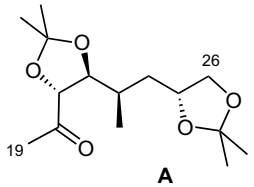
Acknowledgements

Financial support has been granted by the Spanish Ministry of Education and Science (Projects CTQ2005-06688-C02-01/02), and by the Consellería d'Empresa, Universitat i Ciencia de la Generalitat Valenciana (Projects GV05/52, ACOMP06/006 and ACOMP06/008). P.F. and J.M. thank the Spanish Ministry of Education and Science for a Juan de la Cierva and a Ramón y Cajal contract, respectively.

References

1. König, G. M.; Kehraus, S.; Seibert, S. F.; Abdel-Lateff, A.; Müller, D. *ChemBioChem* **2006**, *7*, 229–238.
2. For reviews partially or totally related to the chemistry and/or biology of amphidinolides, see: (a) Kobayashi, J.; Ishibashi, M. *Chem. Rev.* **1993**, *93*, 1753–1769; (b) Maranda, L.; Shimizu, Y. *J. Phycol.* **1996**, *32*, 873–979; (c) Ishibashi, M.; Kobayashi, J. *Heterocycles* **1997**, *44*, 543–572; (d) Chakraborty, T. K.; Das, S. *Curr. Med. Chem.* **2001**, *1*, 131–149; (e) Kobayashi, J.; Shimbo, K.; Kubota, T.; Tsuda, M. *Pure Appl. Chem.* **2003**, *75*, 337–342; (f) Kobayashi, J.; Tsuda, M. *Nat. Prod. Rep.* **2004**, *21*, 77–93; (g) Kobayashi, J.; Tsuda, M. *Phytochem. Rev.* **2004**, *3*, 267–274; (h) Kang, E. J.; Lee, E. *Chem. Rev.* **2005**, *105*, 4348–4378.
3. Usui, T.; Kazami, S.; Dohmae, N.; Mashimo, Y.; Kondo, H.; Tsuda, M.; Terasaki, A. G.; Ohashi, K.; Kobayashi, J.; Osada, H. *Chem. Biol.* **2004**, *11*, 1269–1277.
4. (a) Trost, B. M.; Wrobleski, S. T.; Chisholm, J. D.; Harrington, P. E.; Jung, M. *J. Am. Chem. Soc.* **2005**, *127*, 13589–13597; (b) Trost, B. M.; Harrington, P. E.; Chisholm, J. D.; Wrobleski, S. T. *J. Am. Chem. Soc.* **2005**, *127*, 13598–13610.

5. Williams, D. R.; Kissel, W. S. *J. Am. Chem. Soc.* **1998**, *120*, 11198–11199.
6. Williams, D. R.; Meyer, K. G. *J. Am. Chem. Soc.* **2001**, *123*, 765–766.
7. Trost, B. M.; Papillon, J. P. N.; Nussbaumer, T. *J. Am. Chem. Soc.* **2005**, *127*, 17921–17937.
8. The nonnatural antipode of amphidinolide P has also been obtained: (a) Williams, D. R.; Myers, B. J.; Mi, L. *Org. Lett.* **2000**, *2*, 945–948; (b) Chakraborty, T. K.; Das, S. *Tetrahedron Lett.* **2001**, *42*, 3387–3390.
9. For a review on syntheses of members of the amphidinolide T group, see: Colby, E. A.; Jamison, T. F. *Org. Biomol. Chem.* **2005**, *3*, 2675–2684.
10. Ghosh, A. K.; Gong, G. *J. Org. Chem.* **2006**, *71*, 1085–1093.
11. Lepage, O.; Kattnig, E.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 15970–15971.
12. Similar fragments of amphidinolide H and of the closely related amphidinolide H2 have been prepared using other methodologies: (a) Chakraborty, T. K.; Suresh, V. R. *Tetrahedron Lett.* **1998**, *39*, 7775–7778; (b) Liesener, F. P.; Kalesse, M. *Synlett* **2005**, 2236–2238; (c) Liesener, F. P.; Jannsen, U.; Kalesse, M. *Synthesis* **2006**, 2590–2602.
13. Herdeis, C.; Lütsch, K. *Tetrahedron: Asymmetry* **1993**, *4*, 121–131 (corr., *Tetrahedron: Asymmetry*, **1993**, *4*, 151).
14. (a) Gringore, O. H.; Rouessac, F. P. *Org. Synth. Coll. Vol. VII* **1990**, 99–102; (b) Herdeis, C. *Synthesis* **1986**, 232–233.
15. (a) Hanessian, S.; Murray, P. J. *Tetrahedron* **1987**, *43*, 5055–5072; (b) Beach, J. W.; Kim, H. O.; Jeong, L. S.; Nampalli, S.; Islam, Q.; Ahn, S. K.; Babu, J. R.; Chu, C. K. *J. Org. Chem.* **1992**, *57*, 3887–3894.
16. Partial desilylation takes place during lithium enolate methylation. Thus, resilylation of the reaction mixture in situ gives rise to improved yields in **6**.
17. See also: Martin, S. F.; Dwyer, M. P.; Hartmann, B.; Knight, K. S. *J. Org. Chem.* **2000**, *65*, 1305–1318.
18. Resilylation in situ of the reaction mixture gives rise to improved yields of **7**.
19. (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547; (b) Markó, I. E.; Svendsen, J. S. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 2000; Vol. II, Chapter 20.
20. Laganis, E. D.; Chenard, B. L. *Tetrahedron Lett.* **1984**, *25*, 5831–5834.
21. Collier, P. N.; Campbell, A. D.; Patel, I.; Raynham, T.-M.; Taylor, R. J. K. *J. Org. Chem.* **2002**, *67*, 1802–1815.
22. None of the intermediates en route towards **1** nor compound **1** itself were crystalline. Therefore, X-ray analyses aimed at configurational confirmation could not be performed. However, the key asymmetric transformation used here (Sharpless dihydroxylation) is a well-known process with a safely predictable stereochemical outcome. We are thus confident that the structure of synthetic intermediate **1** is that depicted in Scheme 2. Furthermore, a comparison of $^{1}H/^{13}C$ NMR chemical shift and coupling constant values within a similar fragment **A**[12b] (see table below, the atom numbering of Scheme 1 is also used for **A**, coupling constant values are given in parentheses) gives support to our structural assignment (the observed differences can be accounted for with the different protecting groups at one end of the carbon chain).



A

Atom	**1**	**A**[12b]	Atom	**1**	**A**[12b]
H-19	2.25 s, 3H	2.27 s, 3H	C-19	27.0	27.0
H-21	4.11 d (7)	4.07 d (7.3)	C-20	208.8	209.2
H-22	3.98 dd (7, 5.5)	4.01 dd (7.3, 4.4)	C-21	83.4	83.0
H-23	1.95 m	2.04–1.95 m	C-22	82.2	81.3
H-24	1.58 ddd (13.5, 10, 3)	1.72 ddd (13.7, 9.1, 4.4)	C-23	31.8	32.5
H-24′	1.48 m	1.42–1.35 m	C-24	38.5	37.6
H-25	3.75 m	4.17 dddd (8.9, 7, 5.9, 4.1)	C-25	70.6	73.8
H-26	3.59 dd (10, 5)	4.04 dd (8, 6.1)	C-26	68.2	69.8
H-26′	3.44 dd (10, 7)	3.49 dd (7.7, 7.3)	MeC_{23}	14.4	13.8
MeC_{23}	1.00 d, 3H (6.6)	1.00 d (6.8)	Me_2C (acetal)	110.2	110.2
				26.5	26.5
				26.3	26.1
Me_2C (acetal)	1.45 s, 3H	1.44 s (3H)	TES	6.8 (CH_3)	—
	1.39 s, 3H	1.38 s (3H)		5.0 (CH_2)	
TES	0.88 t, 9H (8)	—	TBDPS	135.7 (CH)	—
	0.50 q, 6H (8)			133.7 (C)	
				133.6 (C)	
				129.6 (CH)	
				127.7 (CH)	
				26.9 (CH_3)	
				19.2 (C)	
TBDPS	7.70–7.65, 4H, m	—			
	7.45–7.35, 6H, br m	—			
	1.05 s, 9H	—			